

International State of the Science Meeting on Blast Induced Tinnitus  
Chantilly, Virginia, November 15-16, 2011

# **Tinnitus – a combination of noise trauma and damage to medial prefrontal cortex?**

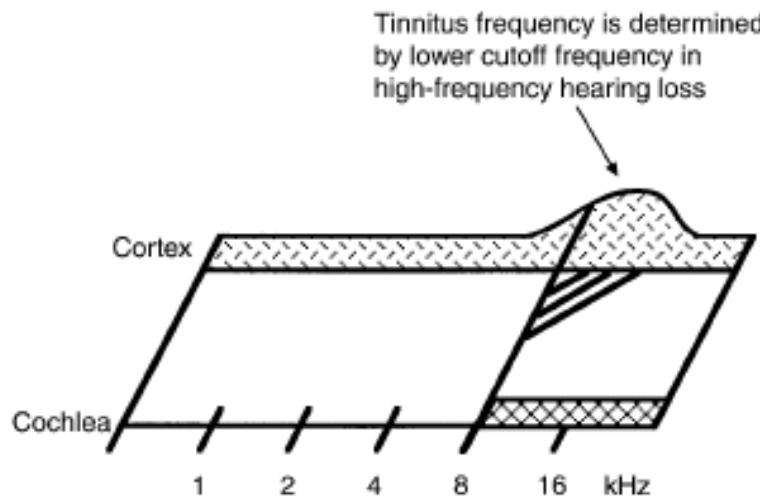
Josef P. Rauschecker

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Georgetown University Medical Center  
Washington, DC, USA

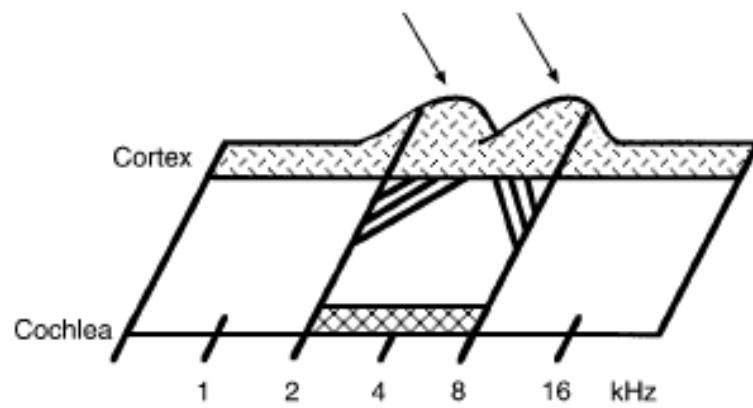
# Auditory Components

C

## Tinnitus model



Tinnitus consists of complex sound with two (or more) frequency bands



cortical locus

lesion in cochlea

# Cortical Reorganization in Tinnitus: Lesion-Induced Plasticity in Auditory Cortex

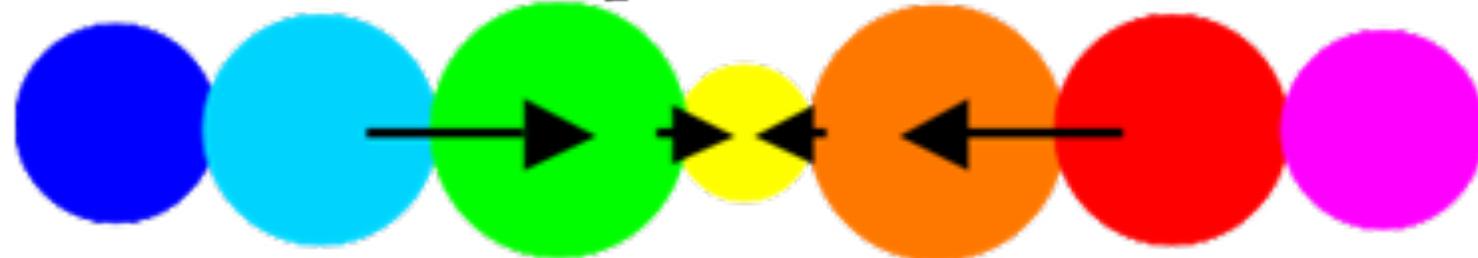
Rauschecker,  
*TINS*, 1999

# “Remapping” in Auditory Cortex after Sensorineural Hearing Loss

*Normal Tonotopic Map:*

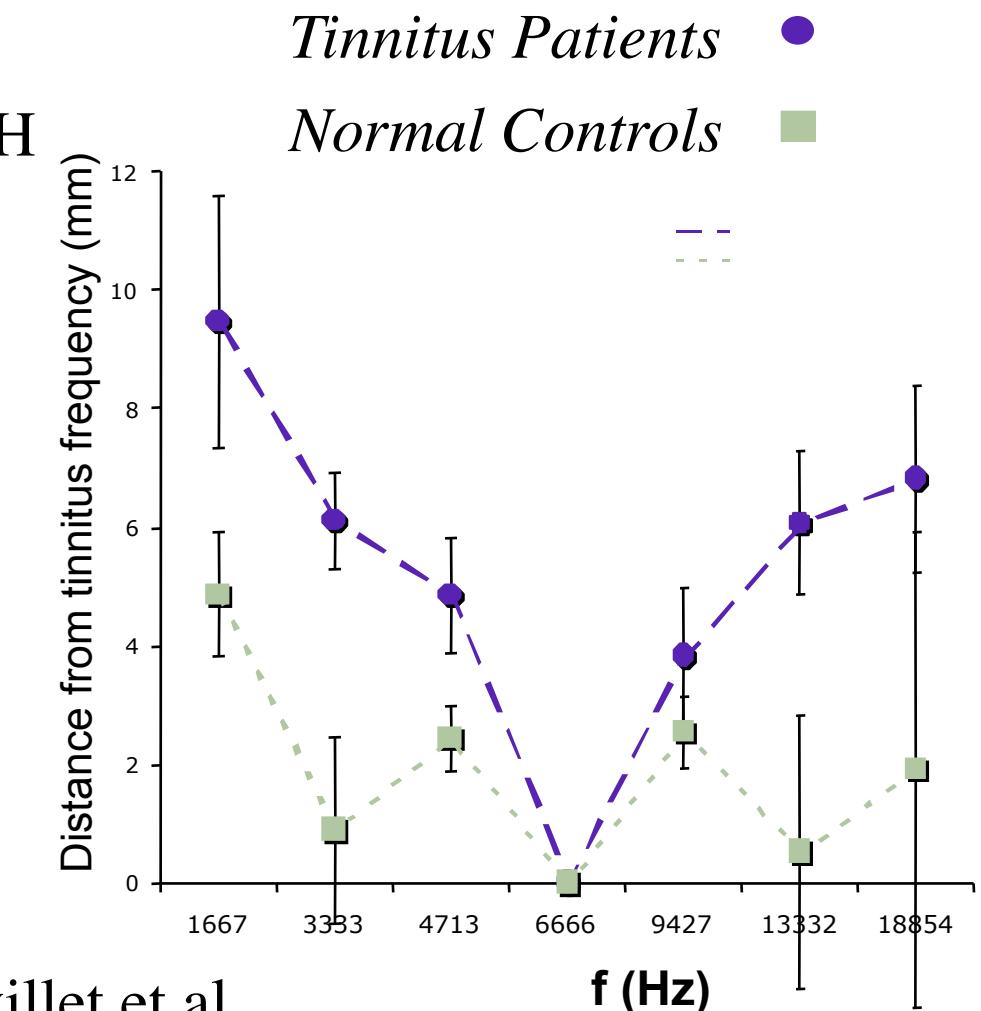
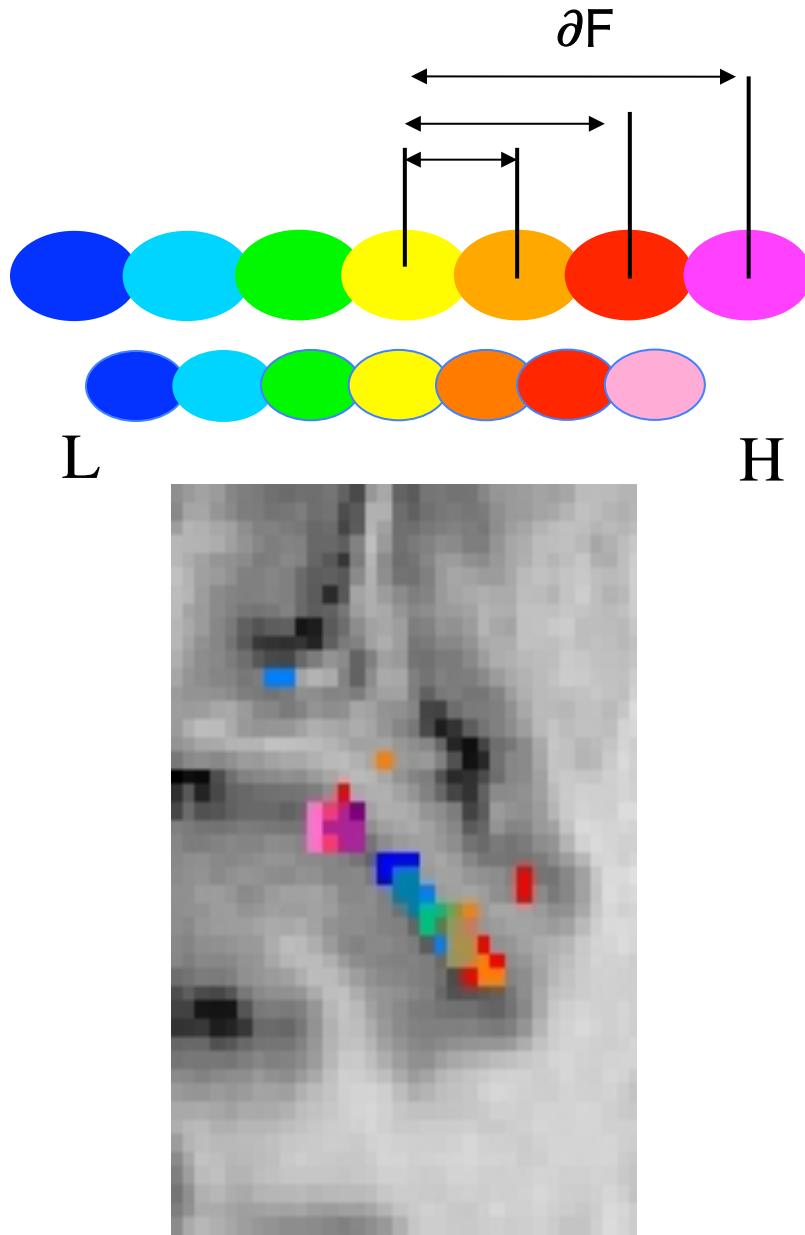


*Hypothesized Reorganization After Tinnitus:*



**Lesion frequency**

# Functional MRI of Auditory Cortex



with Amber Leaver, Mark Chevillet et al.

# Time course of auditory remapping

Hours:

Noreña AJ, Tomita M, Eggermont JJ (2003)  
J Neurophysiol 90: 2387-2401.

Months:

Cheung SW, Bonham BH, Schreiner CE, Godey B,  
Copenhaver DA (2009) J Neurosci 29: 7065-7078.

# Structural Brain Changes in Tinnitus

Mühlau, Rauschecker et al.  
*Cerebral Cortex* 16(9), 1283-1288 (2006)

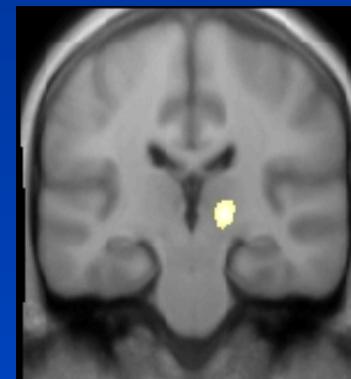
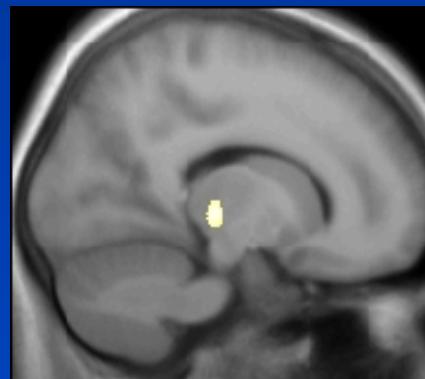
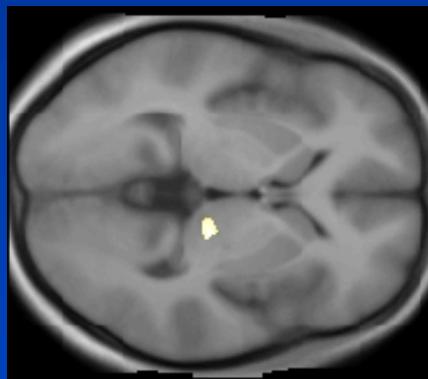
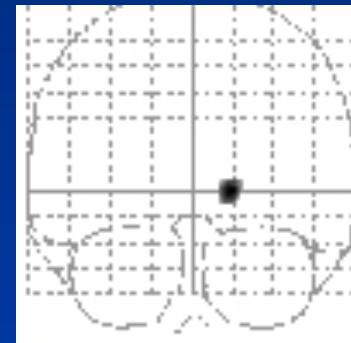
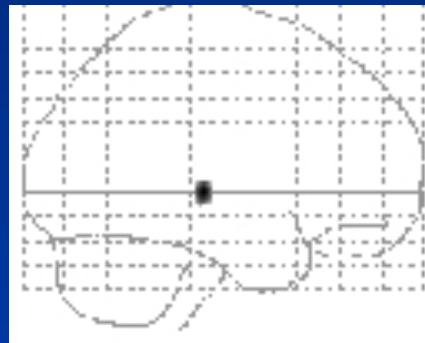
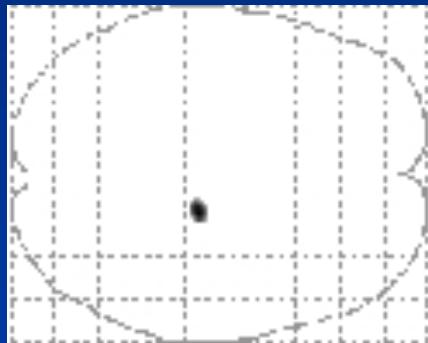
# Voxel-Based Morphometry

- High-resolution structural MRI
- Gaussian random fields
- SPM2 (Good et al., 2001)
  - grey-matter **density**
  - grey-matter **volume**

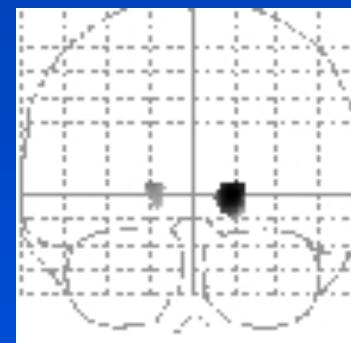
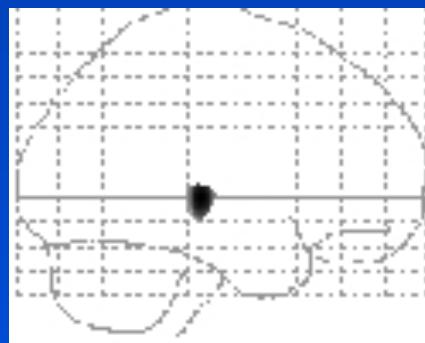
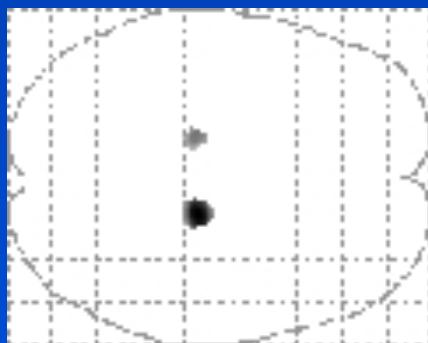
Our study:

- 28 tinnitus patients (age: 25-55 years)
- 28 controls paired for age and gender

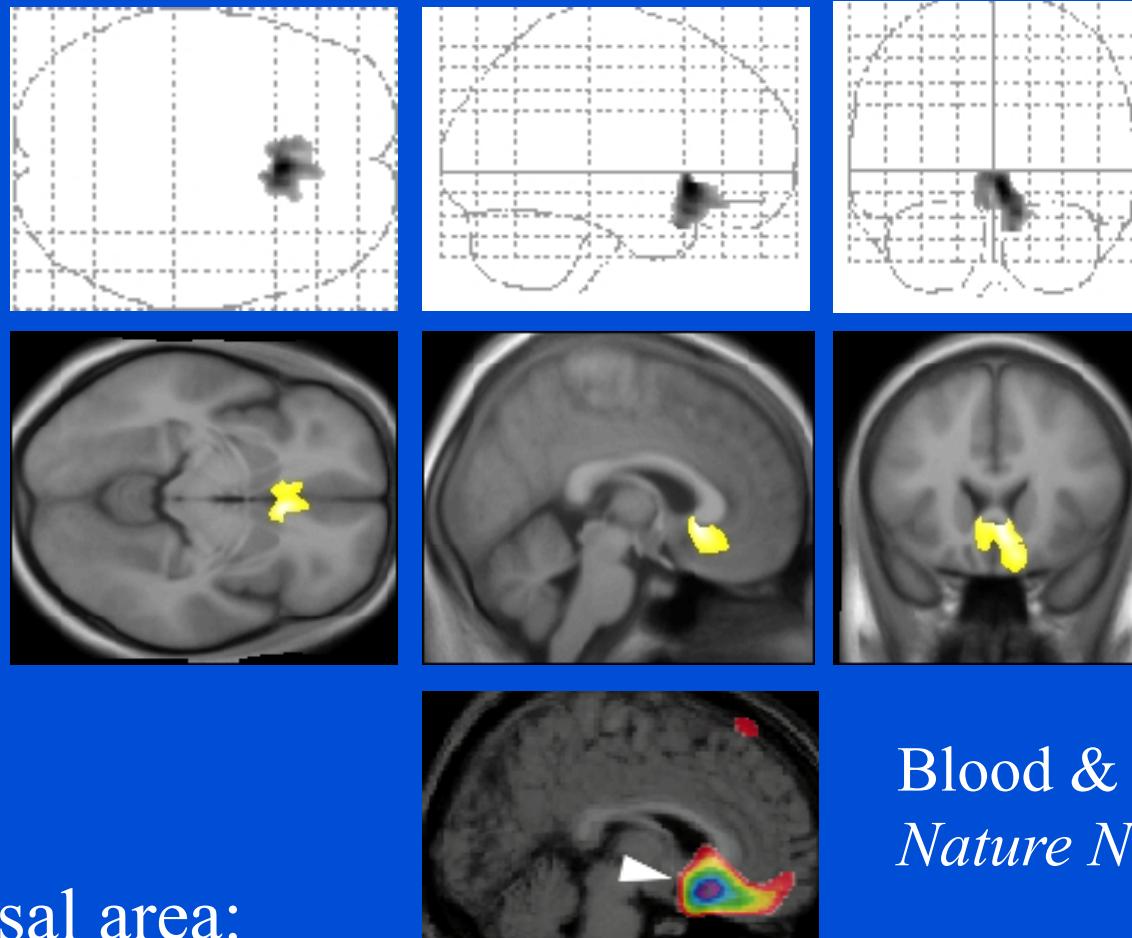
# Density Increase in Auditory Thalamus $z = 3.8$ ; $p < 0.05$ corrected



No change  
in auditory  
cortex



# Volume Decrease in Paralimbic Regions $z = 4.9$ ; $p < 0.05$ corrected



Blood & Zatorre,  
*Nature Neuroscience* 1999

Subcallosal area:

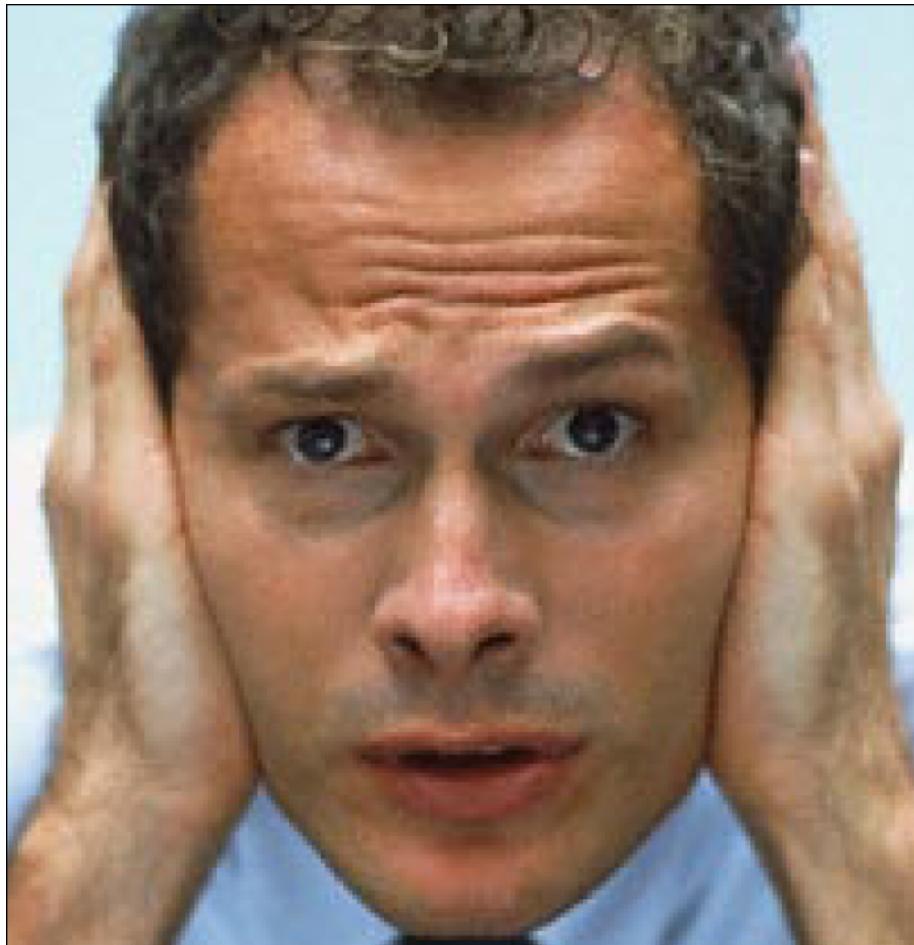
Ventromedial prefrontal cortex (vmPFC); n. accumbens (NAc)

# Nonauditory Components

# The Case of the Loud Eyeballs

In which a mystery is solved through a chance encounter

BY R. DOUGLAS FIELDS



# Nonauditory Factors

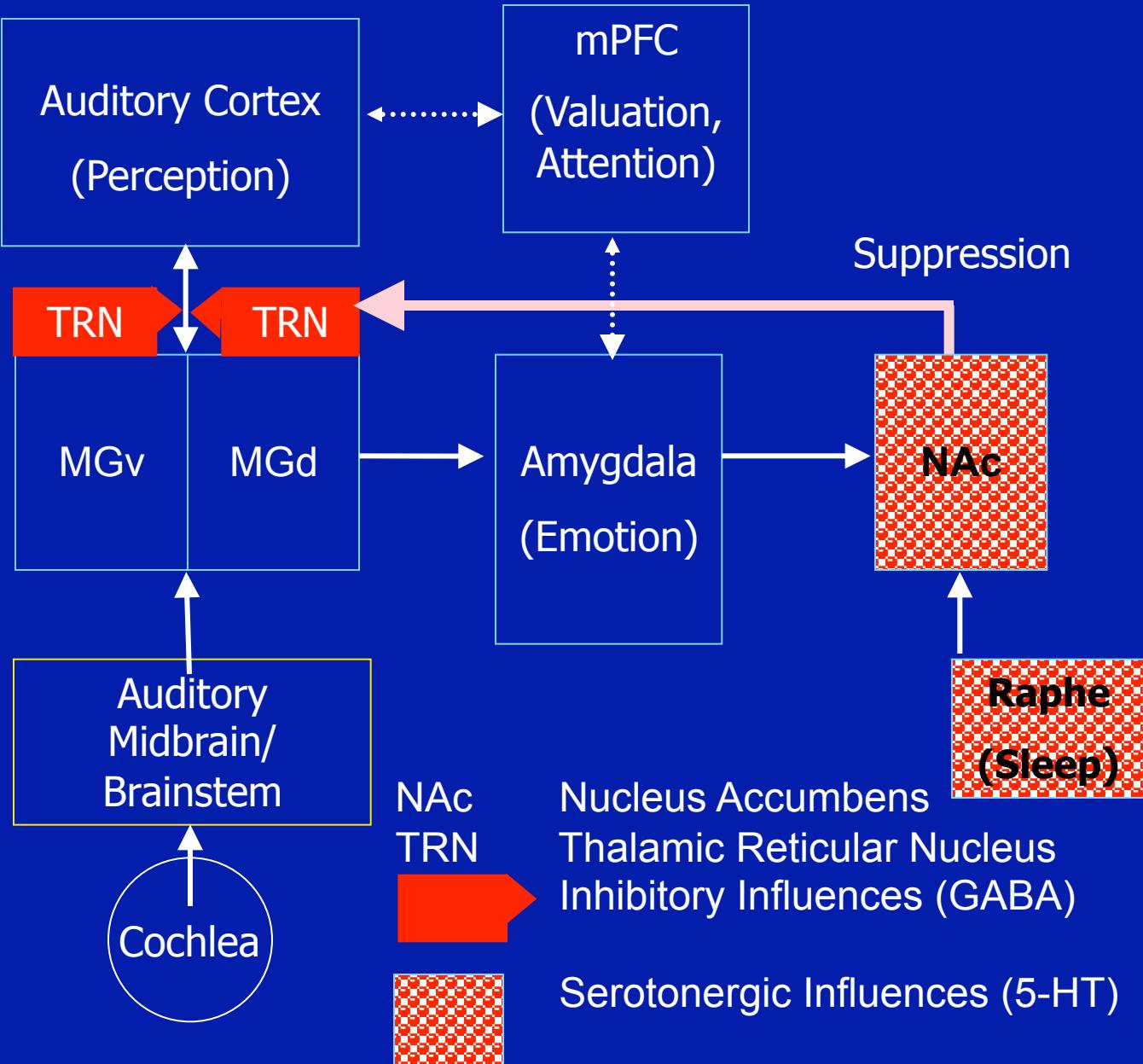
- Not every person with hearing loss gets tinnitus
- Intermittent Tinnitus
  - Stress
  - Sleep Deprivation, Insomnia
  - Depression, Dysphoria
- Limbic System Involvement
  - Jastreboff: Pavlovian Fear Conditioning
  - Lockwood/Salvi: PET Studies
  - Wallhäusser-Franke et al.: Animal Studies

# Limbic System Involvement: Reaction or Cause?

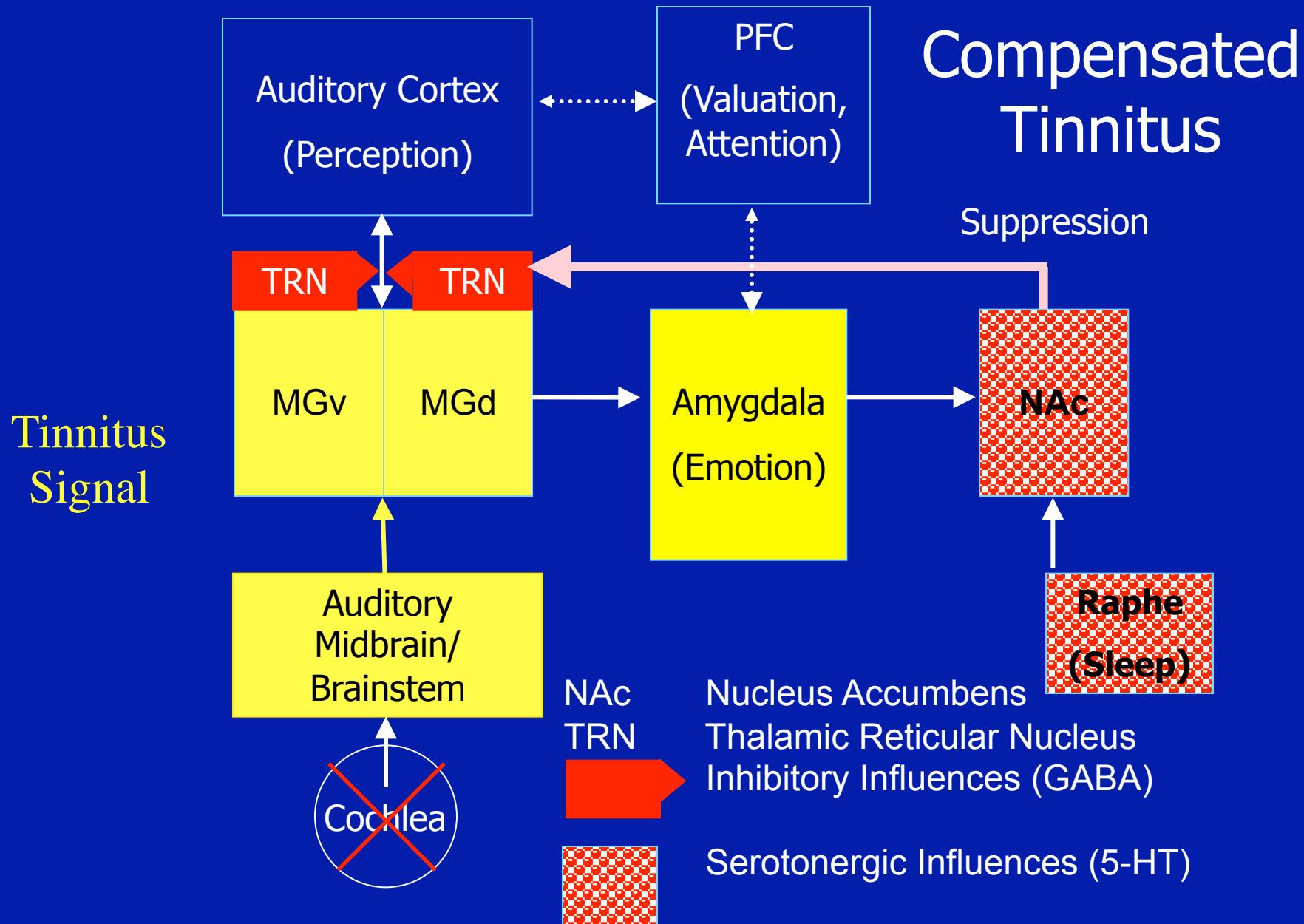
# Tuning out the Noise: Auditory-Limbic Interactions in Tinnitus

Rauschecker, Leaver, Mühlau  
*Neuron* 66 (6), 819-826 (2010)

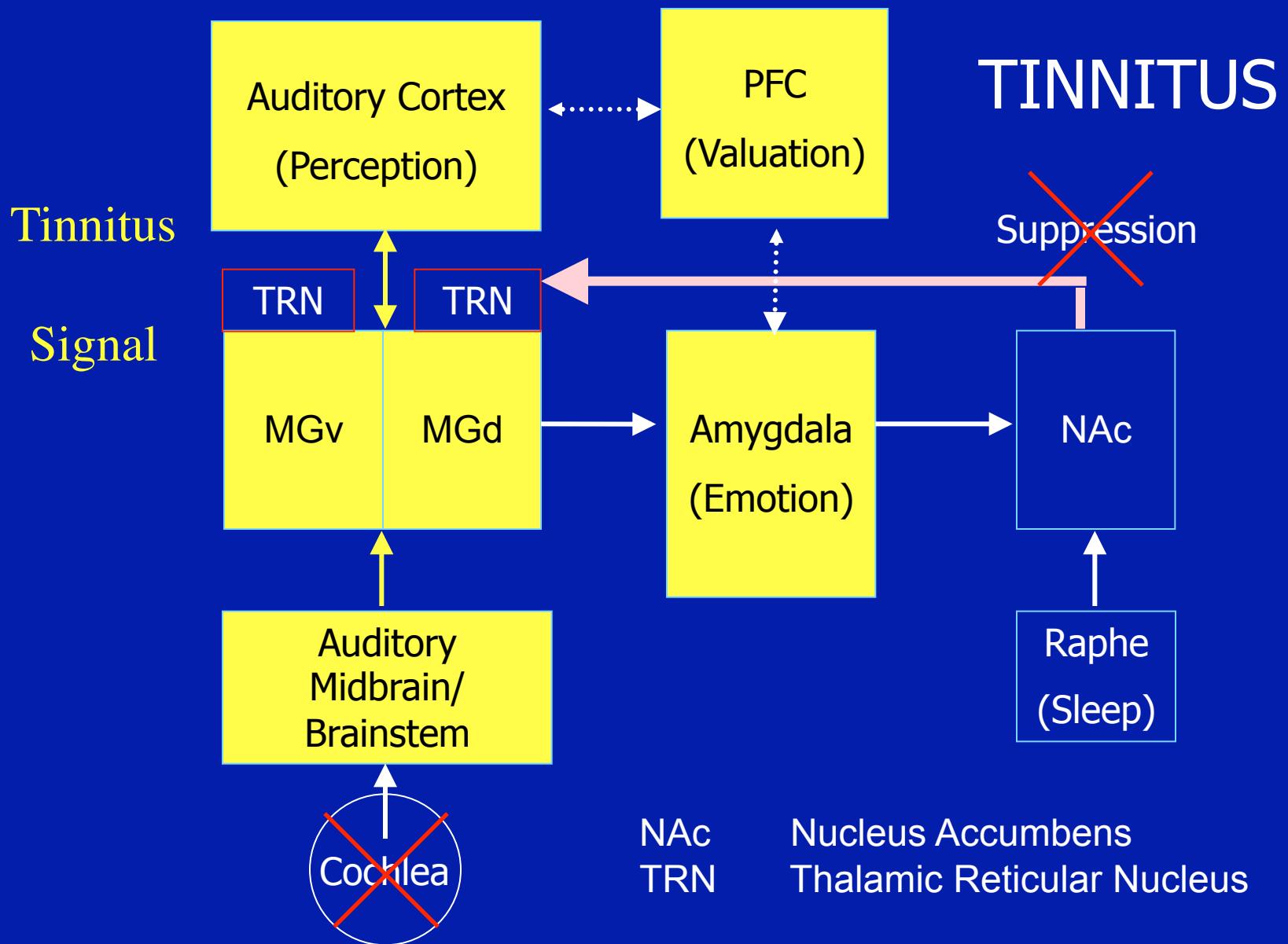
# Normal Hearing + Normal Limbic System



# Abnormal Hearing + Normal Limbic System



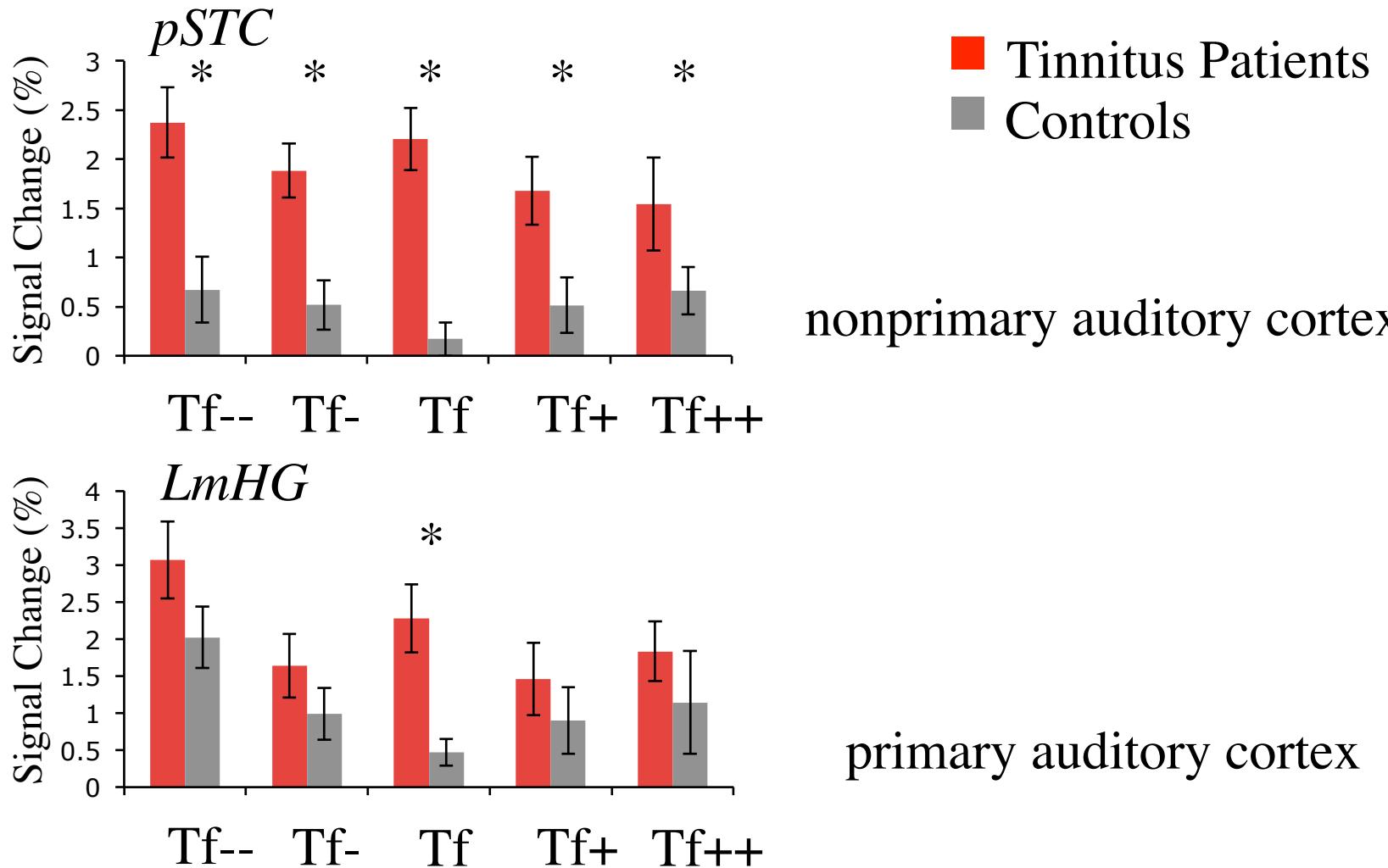
# Abnormal Hearing + Abnormal Limbic System



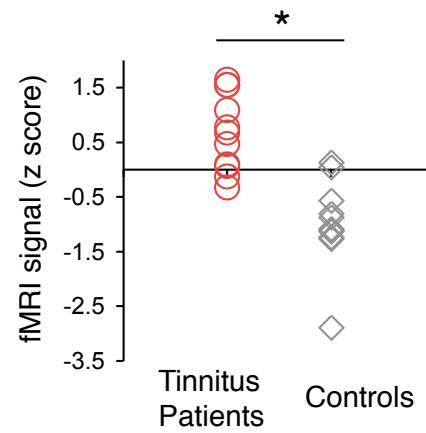
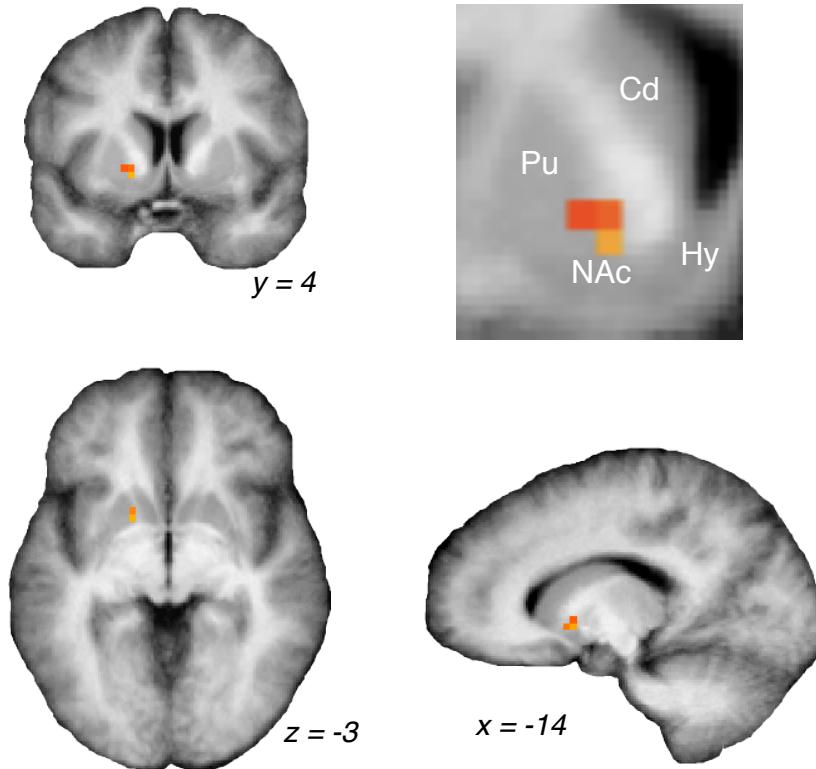
# Dysregulation of Limbic and Auditory Networks in Tinnitus

Leaver, Renier, Chevillet, Morgan, Kim, Rauschecker  
Neuron 69(1), 33-43 (2011)

# Hyperactivity in Auditory Cortex

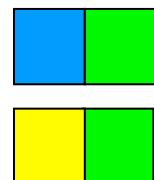
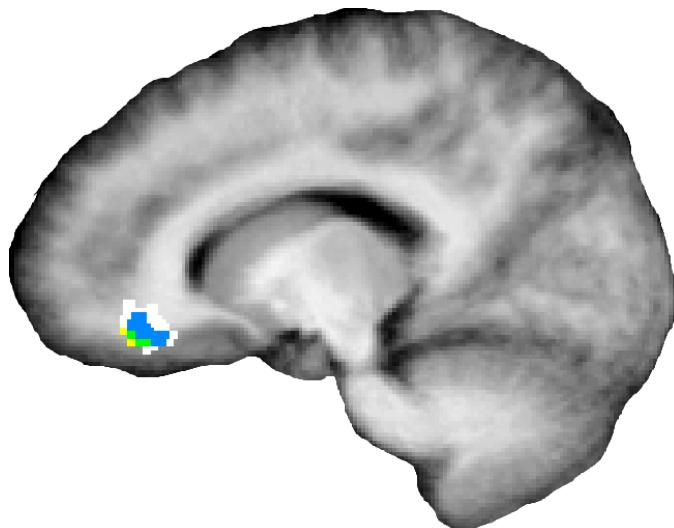


# Functional MRI: Hyperactivity in Nucleus Accumbens



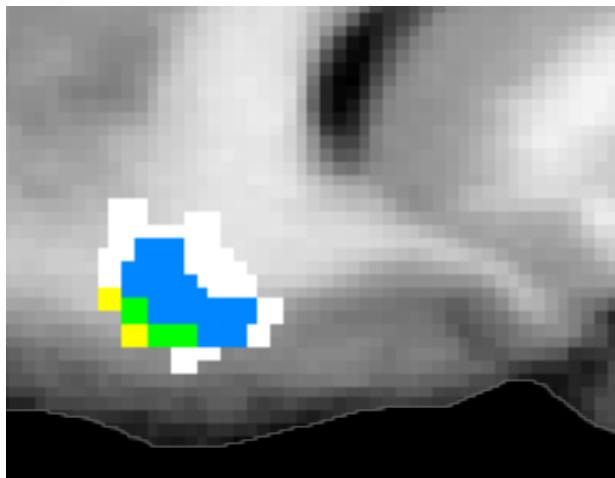
$p < 0.00005$

# Structural MRI: Voxel-Based Morphometry



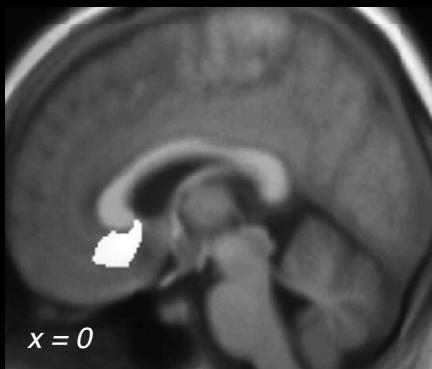
GM Amount/“Volume” Decrease

GM Concentration/“Density” Decrease

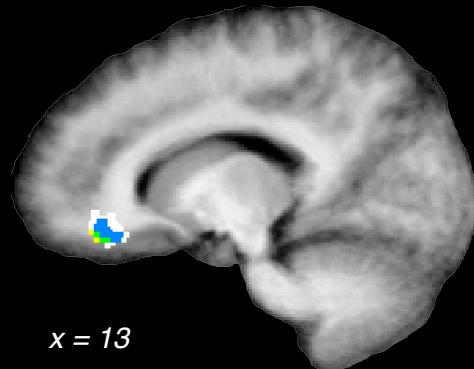


Ventromedial  
prefrontal cortex  
(vmPFC)

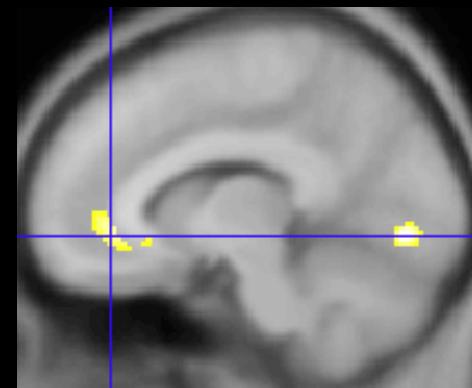
# *MRI: Structural differences in the limbic system*



Mühlau et al. 2006 Cerebral Cortex

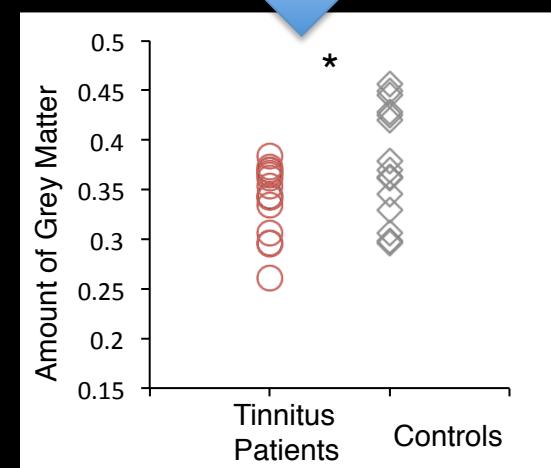
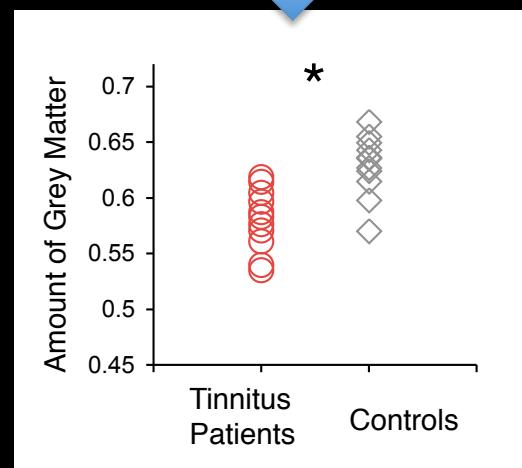


Leaver et al. 2011 Neuron

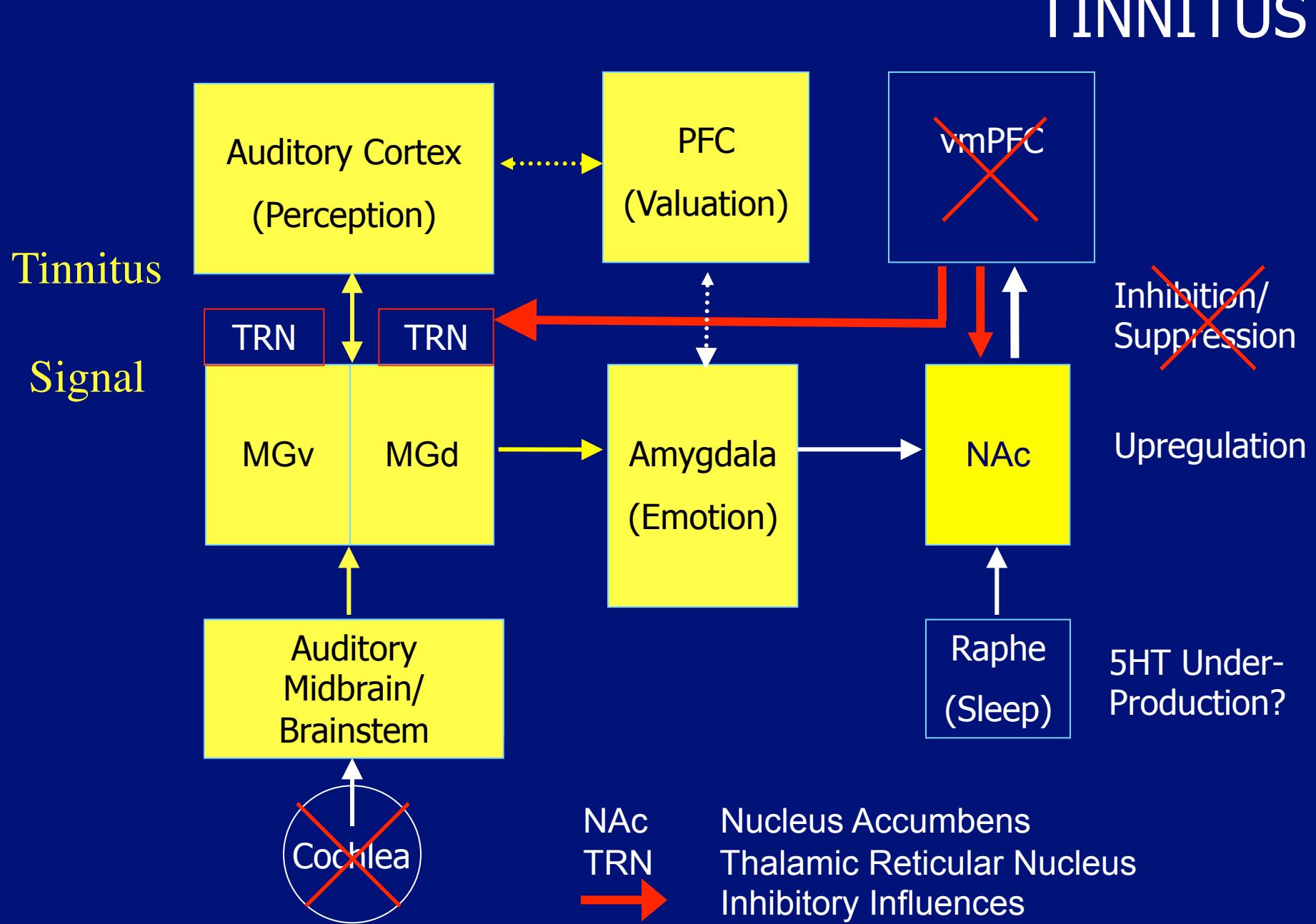


Leaver et al. (unpublished data)

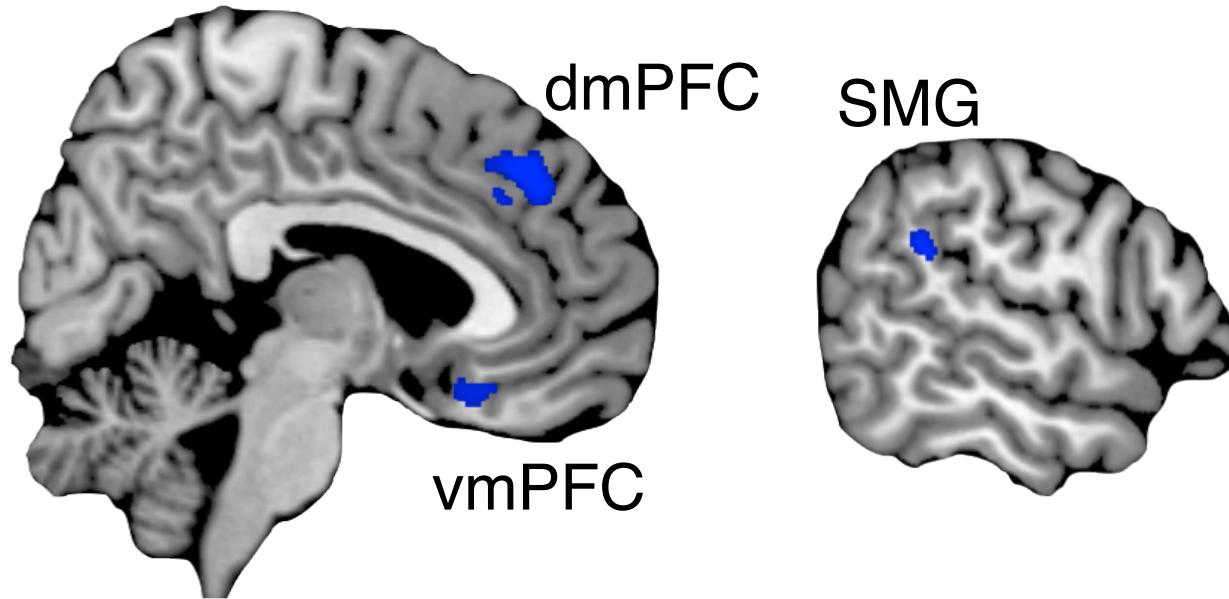
In 3 independent samples, tinnitus patients have, on average, less grey matter than controls in ventromedial prefrontal cortex (vmPFC).



# TINNITUS

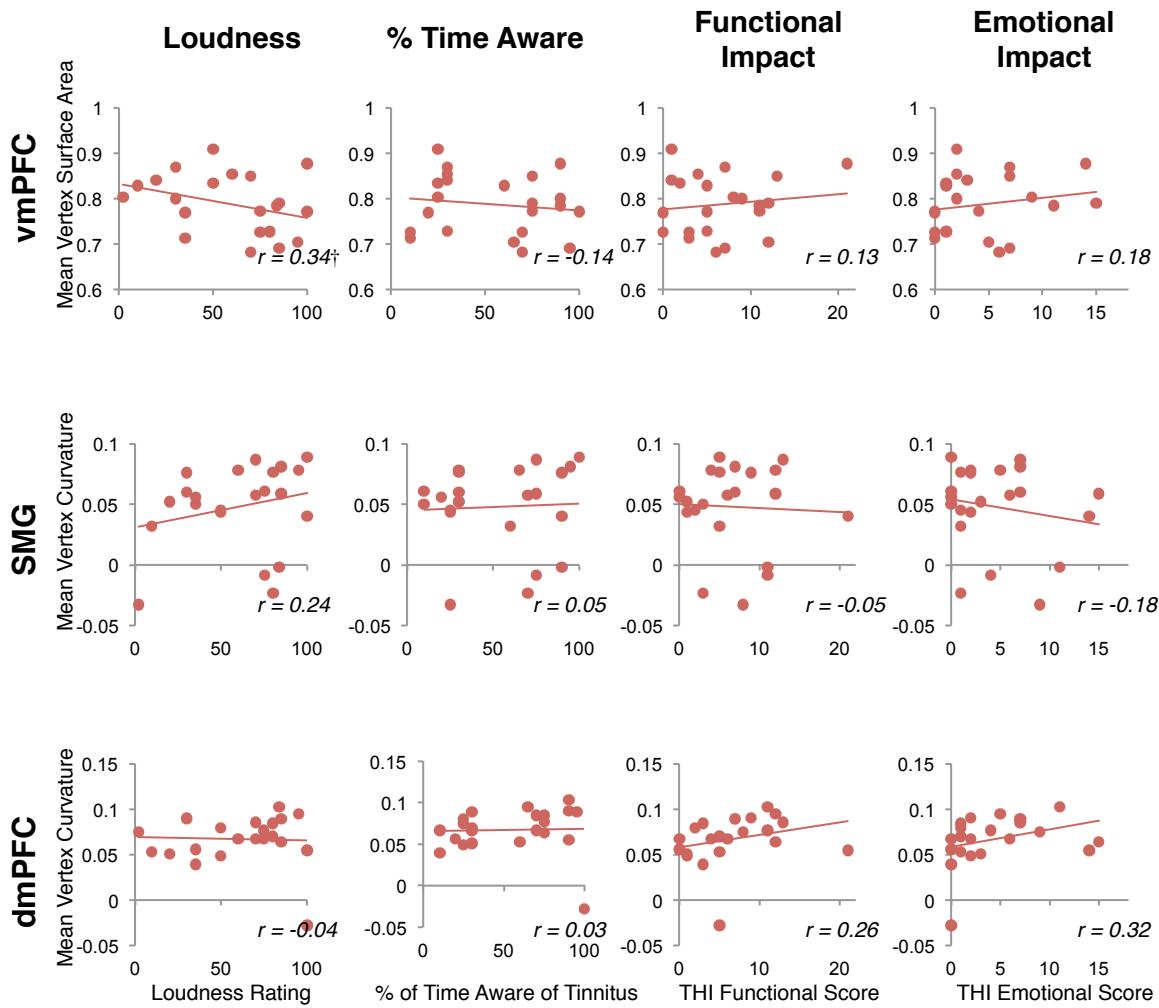


# Structural Damage in Tinnitus Patients (II): DARTEL-VBM analysis

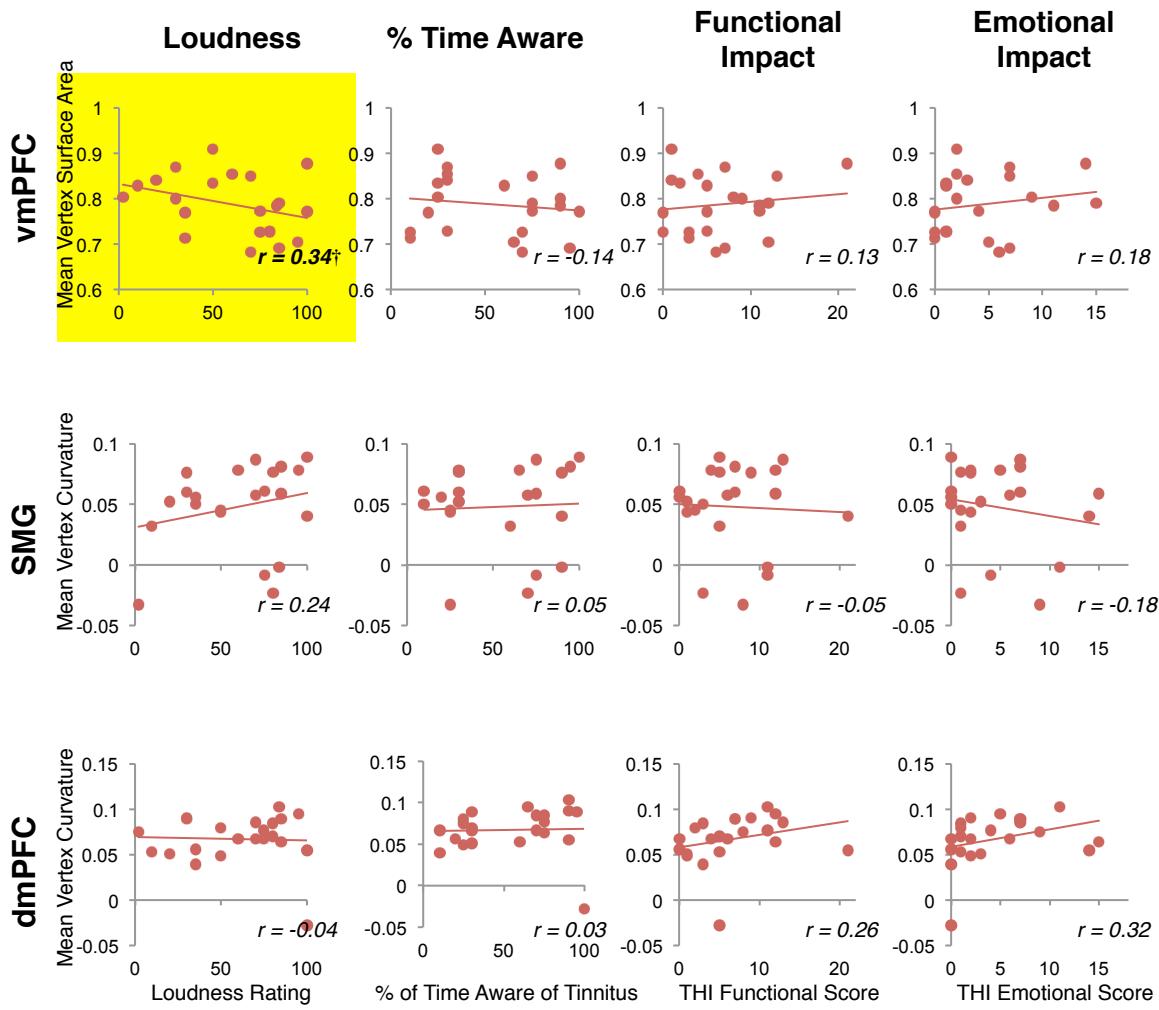


$p < 0.002, k > 350 \text{ mm}^3$

# Tinnitus Characteristics



# Tinnitus Characteristics



# Conclusions

Tinnitus is the conjunction of two pathologies:

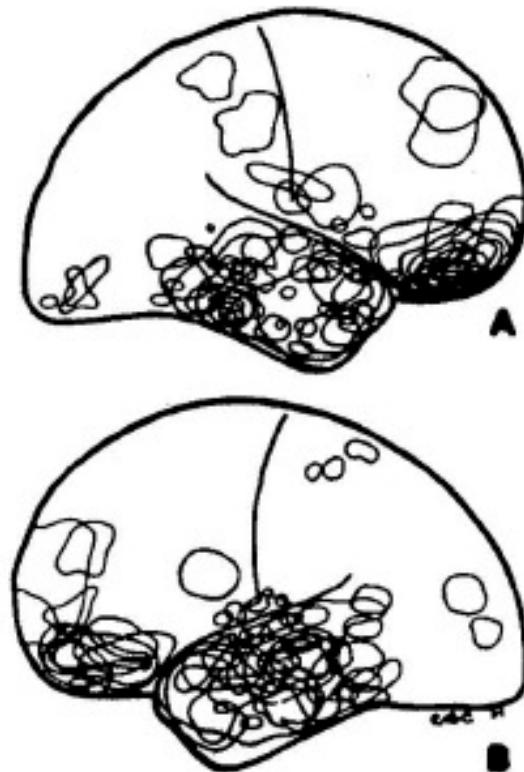
- 1) Auditory (bottom-up): Peripheral auditory damage followed by central auditory changes
- 2) Limbic-frontal (top-down): Lack of limbic suppression due to medial frontal damage

Military personnel is exposed to  
both risk factors:

- 1) Loud-noise exposure
- 2) Operational stress

# Possible Link with TBI/Blast-Injury

# Frontal Lobe Dysfunction following Closed Head Injury



Those brain areas most commonly affected by TBI (especially ventral prefrontal cortex) are also the key players in our tinnitus model.

FIG. 1. Contusions sustained in 40 consecutive cases of traumatic brain injury. The tendency for maximal pathology in the orbital frontal and temporal regions is clearly depicted. (From Courville, CB. *Pathology of the central nervous system*. Mountain View, CA: Pacific Publishers, 1937; reproduced with permission.)

# Frontal lobe changes after severe diffuse closed head injury in children: a volumetric study of magnetic resonance imaging

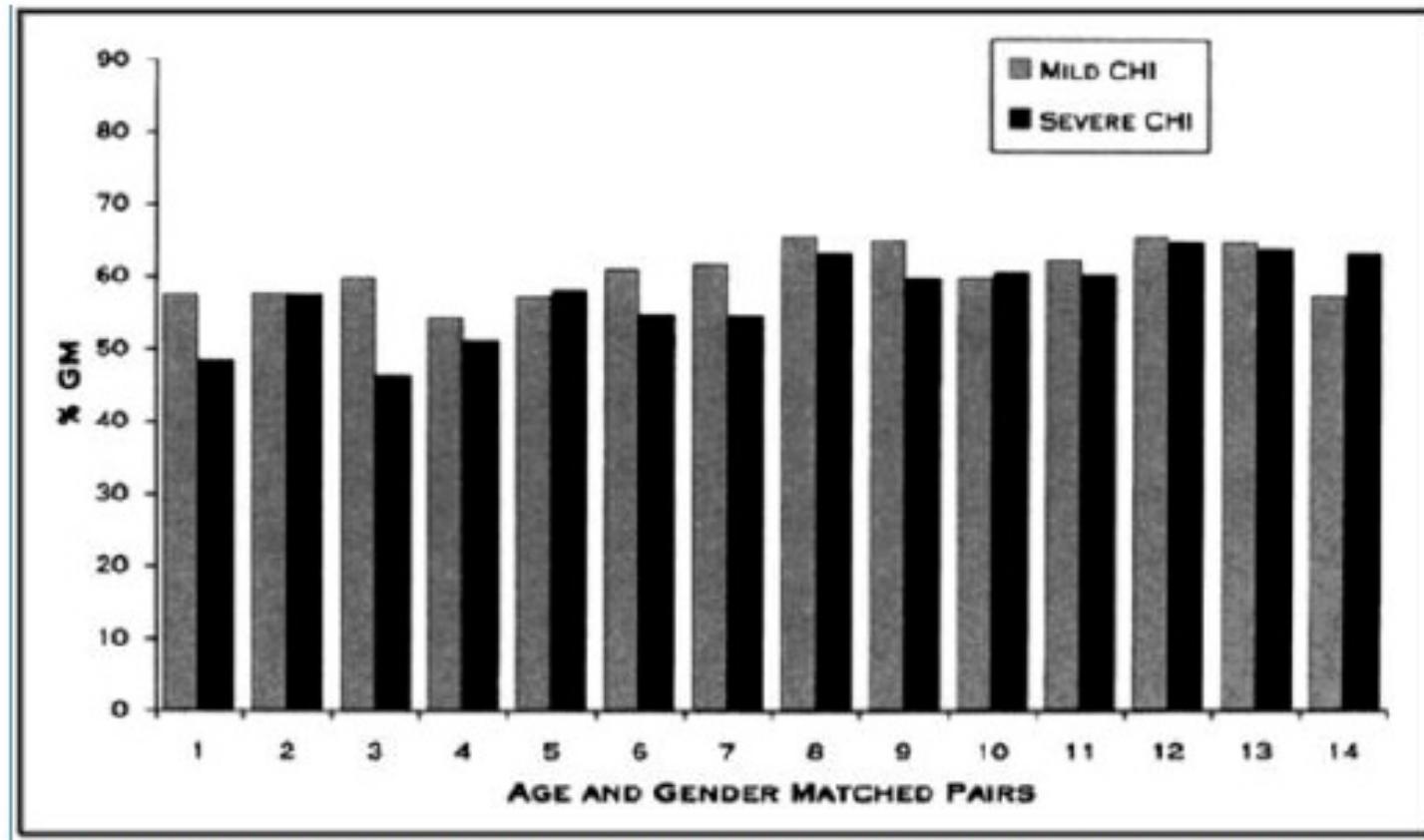
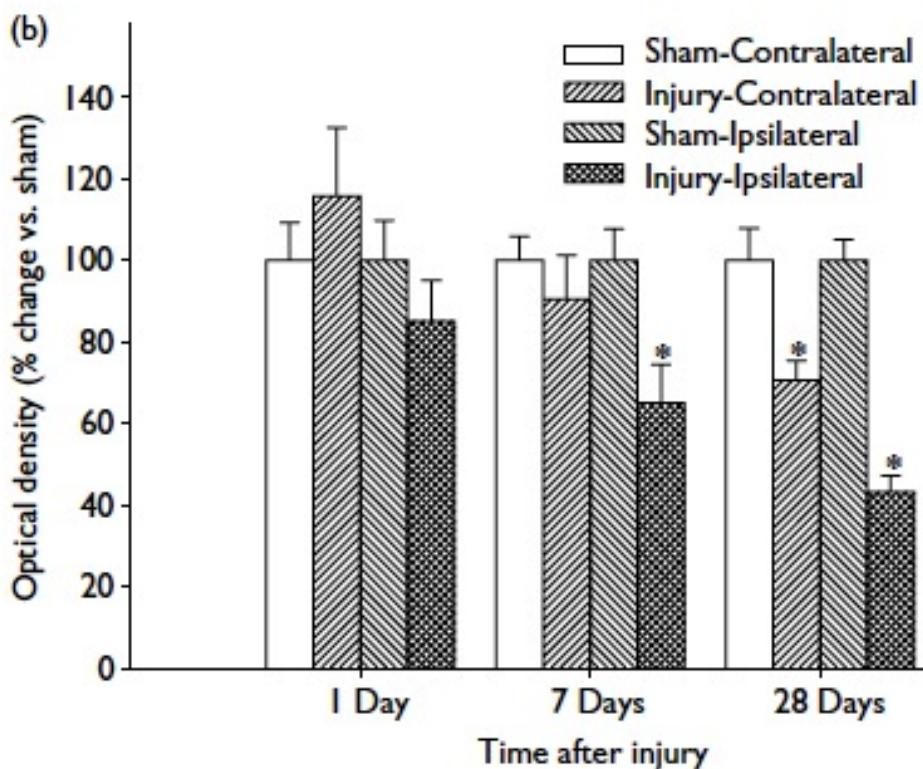


Figure 2. Prefrontal GM expressed as a percentage of total prefrontal intracranial volume and plotted for pairs of severely and mildly head-injured children who were matched on gender and age at MRI.

# Traumatic brain injury reduces dopamine transport expression in the rat frontal cortex



Western blot analysis demonstrates a chronic decrease in dopamine transporter (DAT) protein in rat frontal cortex after unilateral TBI.

Military personnel is exposed to all three risk factors:

- 1) Loud-noise exposure
- 2) Operational stress
- 3) TBI to frontal lobe

# Future Studies

- Diagnosis: Human imaging
- Prevention: Identify high-risk individuals
- Treatment: DBS of NAc; drug treatment
- Nonhuman primate studies:
  - Larger brain
  - Highly developed frontal cortex
  - Top-down modulation

# **COLLABORATORS**

## **Functional Imaging:**

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**Laurent Renier**

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**Christian Gaser**

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**Hung Jeffrey Kim**

**Susan Morgan**

## **Psychiatry:**

**Steve Epstein**

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